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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,423	10/16/2001	Avi J. Ashkenazi	GNE.2630P1C21	5291

7590 05/28/2004

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,423	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's April 01, 2004 response is acknowledged. In view of the amendment, claim 63 has been cancelled. Claims 58-62 are currently pending and under examination.

Priority

2. Applicant's arguments concerning the accordance of priority to the instant application has been fully considered, however the instantly claimed invention is accorded the effective filing date of **10/16/2001**.

Applicant submits that the instant application should be accorded the same effective filing date of February 18, 2000 as that of application 09/978802.

3. The Examiner the discrepancy between the assignment of priority to the instant application and application 09/978802, which teaches the protein to which the instantly claimed antibody binds; however, upon further consideration of the claims and the instantly claimed invention, it is determined that the protein to which the antibody binds lacks a utility. The reasons for lacks of utility was presented in the previous office action and additionally set forth below. Therefore, the priority that was previously granted to the instant application in the previous office action is hereby withdrawn, the same will take place for application 09/978802, because upon further consideration the instant invention lacks a utility.

Specification

4. Applicant's amendment's to the specification to correct i) a spelling error, ii) use of hyperlinks, iii) deposit rules, and iv) abstract has been acknowledged and entered.

Claim Objections

5. The objection of claim 63 as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of Applicant's amendment, canceling claim 63.

Claim Rejections - 35 USC § 101

6. Claims 58-62 remains rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicant's response has been fully considered, however, it was found not persuasive.

Applicant submits that the instantly claimed antibody complied with the utility requirement, because the Examiner had acknowledged that the protein, which is claimed in 09/978802, which the claimed antibody binds meets the utility requirement.

The Examiner acknowledges the discrepancy. However, it has been determined that the protein to which the antibody bind lacks a utility. The reasons for lacks of utility was presented in the previous office action and additionally set forth below. The Examiner truly apologizes for the inconvenience this may cause Applicant. However, as noted, the protein to which the claimed invention binds, the disclosure in the specification and priority documents, and the teaching of the art; it has been concluded

that the instantly claimed invention and the protein to which it binds do not meet the utility requirement.

As stated in the previous office action, the instantly claimed invention is directed to antibodies that specifically bind to a disclosed polypeptide, SEQ ID NO: 375.

Applicant's assertion that the claimed antibody can be used in diagnostic assays for the disclosed polypeptide, e.g., detection its expression in specific cells, tissues, or serums (line 32-35, page 224, specification), is not specific and substantial utility for the antibody. The antibody lacks a specific and substantial utility because nowhere in the specification has Applicant indicate a specific and substantial utility for the polypeptide that is detected by the antibody of the instant invention.

It is acknowledged that Applicant teaches that the polypeptide to which the instantly claimed antibody binds tested positive in two assays. The first assay is the inhibitory activity in mixed lymphocyte reaction (MLR) assay, assay 67, Example 130. The other assay is the Rat DRG neuronal survival inhibition assay.

However, the inhibitory activity in mixed lymphocyte reaction (MLR) assay does not support a specific and substantial utility for the claimed invention. The ability to stimulate or inhibit lymphocyte proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial (page 354, line 10-11) is not specific since there are many such conditions, and it is not predictable of which conditions the claimed

invention may function, if any.

Mixed lymphocyte culture (MLC) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. MLC is a functional assay of cellular response to stimulatory determinants associated predominantly with HLA class II molecules. A single genetic locus or region, known as HLA, controls the MLC reactivity. The MLC assay recognizes disparate HLA class II molecules and the resulting T-cell activation, which is thought to represent an *in vitro* model of the afferent arm of the *in vivo* allograft reaction. The degree of reactivity observed correlates with the degree of antigenic disparity between responding and stimulating cells. Briefly, when the lymphocytes of 2 HLA-disparate individuals are combined in tissue culture, the cells enlarge, synthesize DNA, and proliferate, whereas HLA-identical cells remain quiescent. Since both cells will normally proliferate, a one way test is used to monitor the response of a single responder cell by inactivating the stimulator cell by radiation or drugs in order to inhibit DNA synthesis of the stimulator cell. The proliferation is driven primarily by the differences in the class II HLA antigens between the 2 test cells (or individuals). This reaction is not predictive of general responses of the immune system because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. All T cells must cooperate with antigen-presenting cells, whereas B cells and cytotoxic T cells depend on helper T lymphocytes. These interactions either require direct surface-to surface contact or are mediated by cytokines that act only over extremely short distances. Because of this interdependence, lymphocyte activation occurs commonly

and efficiently in the secondary lymphoid organs, where lymphocytes, antigens, and antigen-presenting cells encounter one another at close quarters. See pages 30-31, 208-209, 246-247 of "Basic and Clinical Immunology," 1994. See also, "Manual of Clinical Laboratory Immunology," 6th Edition at pages 1164-1166.

Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*.

Additionally, difficulties arise in quantification when using MLC as a test for T cell function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibility in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders. When running the MLC assay for

determining histocompatibility for transplantation, autologous controls combining self with irradiated self are necessary to normalize the response of each cell to stimulators. Furthermore, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of determining histocompatibility for transplantation (page 246 in "Basic and Clinical Immunology"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen should include a control response to a pool of allogeneic cells to measure maximum response and an autologous control to ensure low backgrounds.

Therefore, the MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art

recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary.

Additionally, Applicant's assertion that the polypeptide is expected to be useful in the treatment of neurological conditions which are associated with undesirable neural cell proliferation including neuroblastomas, gliomas, glioblastomas, and the like, after the polypeptide tested positive in the rat DRG neuronal survival inhibition assay is not credible.

The Rat DRG neuronal survival inhibition assay does not support a credible

utility for the protein to which the claimed antibody binds. The ability of the protein to which the instantly claimed antibody binds to inhibit the survival of neural cells does not provide for a credible use of the protein because the cells cultured in this assay are not representative of adult neural cells and tumor cells. Applicant's assertion that the protein in which the claimed antibody binds could be useful for the treatment of neuropathic conditions that are associated with undesirable neural cell proliferation including neuroblastomas, gliomas, glioblastomas and the like (lines 17-18, page 361 of the specification) because it tested positive in the instant assay is not credible because of the teachings that is in the art. It is well known in the art that sensory neurons undergo substantial programmed cell death during early embryonic development. (Oppenheim RW. Cell death during development of the nervous system. Annu. Rev. Neurosci. (1991) Vol. 14, pp. 453-501.)

The art also teaches that factors that cause neonatal cell death such as peripheral nerve injury, growth factor withdrawal, ionizing radiation, capsaicin, and sindbis virus infection; do not have the same affect on adult neural cells. Adult neural cells are more resistant to these factors. (Lewis et al. A role for HSP27 in sensory neuron survival. The Journal of Neuroscience, Oct. 1999. Vol. 19(20), pp. 8945-8953.) This teaching exemplifies that the activities observed from this assay for embryonic neural cells are not necessarily representative of adult neural cells and tumor cells. This is further exemplified by Memberg et al., who teaches that the survival of neural cells depends on specific factors and that the factor dependence changes with the age of the neural cells.

Rat DRG neuronal assay has been used known to be used in the art to study the effects of various factors on neural development. However, no art-known nexus exist between the cell growth, embryonic neurons, in this assay and the predicable treatment of neuropathies and undesirable neural cell proliferation. Therefore, without such nexus, the claims lack a credible utility.

Thus, in view of the discussion above, the asserted utility for the polypeptide is not adequate to yield a specific and substantial utility or credible utility for the polypeptide. Therefore, the protein to which the claimed antibody binds lacks a specific and substantial utility or credible utility . Without a specific and substantial utility for the polypeptide, the antibody that binds to the polypeptide also lacks a specific and substantial utility.

7. Claims 58-62 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial or credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24

(CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention is directed to antibodies.

The breadth of the claims encompasses all antibodies that specifically bind to a protein having SEQ ID NO: 375.

One skilled in the art would not know how to use the claimed antibody without an undue burden of experimentation because the protein to which the claimed antibody binds lacks a specific and substantial or credible asserted utility. The specification teaches that the protein to which the claimed antibody binds tested positive for an MLR assay and a rat DRG neuronal assay. However, the data gathered or collected from those assays do not enable one skilled in the art to practice the claimed invention without an undue burden of experimentation because the specification does not teach a specific and substantial or credible utility, which is discussed above, for the protein to which the claimed antibody binds.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 112

8. The rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for claims 58-63 on the grounds that the recitation "specifically binds to" in the claims can imply that the antibody is exclusive of the polypeptide or that the antibody binds to a particular antigenic epitope of the polypeptide, is withdrawn in view of Applicant's cancellation of claim 63.

Claim Rejections - 35 USC § 102

9. The rejection of claims 58-62 under 35 U.S.C. 102(b) as being anticipated by Ichtchenko et al, ("Neuroligin 1: A Splice Site-Specific Ligand for β–Neurexins", 1995) is stands.

Applicant's response has been fully considered, however, it was not found persuasive. Applicant submits that the claimed antibodies that bind specifically to a polypeptide of SEQ ID NO: 375 binds to a unique epitope within such polypeptide. However, Applicant did not identify the unique epitope within such polypeptide. Therefore, the rejection stands, in absence of evidence to the contrary. Ichtchenko et al. remains to anticipate the instantly claimed invention because Ichtchenko et al. teaches a polypeptide that consists of amino acid residues that correspond to an amino acid

epitope of the polypeptide to which the claimed antibody binds. As mentioned in the previous office action, because of common epitope that exists in both polypeptides, it is expected that the antibody that binds to the polypeptide taught by Ichtchenko et al. would bind to the claimed polypeptide, SEQ ID NO: 375.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0169.

E.Le
Emily Le

Shanon Foley
Patent Examiner, AU 1648